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REVIEW

Composite tissue allotransplantation: a review of relevant immunological issues for plastic surgeons

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Received 8 March 2007; accepted 16 November 2007

KEYWORDS

Composite tissue
allotransplantation;
Immunosuppression;
Face transplant;
Hand transplant;
Ethics

Summary *Background:* Composite tissue allotransplantation of hand, facial and other tissues is now a clinical reality. The terminology, treatment principles, drug combinations, dosage schedules and mechanisms of the immunosuppression medications on which contemporary transplant surgery is based are unfamiliar to plastic surgeons and most healthcare providers outside the field of transplantation medicine. With this in mind, the purpose of this manuscript is to provide plastic surgeons with a comprehensive and understandable review of key immunological principles relevant to composite tissue allotransplantation.

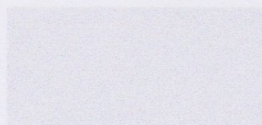
Methods: We present an overview of the immunological basis of composite tissue allotransplantation aimed at the plastic surgery readership, based on our own experience plus manuscripts sourced from MEDLINE, EMBASE, text books, ancient manuscripts and illustrations.

Results: In this manuscript we provide the reader with a brief history of composite tissue allotransplantation (CTA), a concise description of the immunological terminology, treatment approaches, risks associated with immunosuppressive therapy, risk acceptance, and current research avenues relating to contemporary CTA.

Conclusion: Today, as transplant and reconstructive surgeons join forces to move hand and facial tissue allotransplantation into the clinical arena, it is important that plastic surgeons

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have an understanding of the major immunological principles upon which this new treatment is based.

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Composite tissue allotransplantation (CTA) of hand and facial tissues is now a clinical reality. To date, 20 individuals have received seven double hand, 12 single hand and one thumb transplant worldwide. Several of these cases are more than 8 years post transplant and only two graft failures have been reported, one due to noncompliance¹ and the other due to unclear aetiology² (Table 1). Overall the functional outcomes and patient satisfaction have been reported to be good.² In addition, four cases of head and neck allotransplantation have been reported, two in China³ and two in France.^{4–7}

The microsurgical techniques required to successfully transplant hand and facial tissues are well established and are used in daily practice by the plastic surgery community worldwide. The immunosuppression medications used to prevent tissue rejection in these cases are the same as those used in tens of thousands of solid organ transplant recipients and have been extensively studied for many years. The psychosocial and ethical issues associated with these new procedures are being developed as new clinical cases are being performed and followed.

Some of the greatest advancements in the fields of plastic and transplant surgery have been achieved through a close collaboration between plastic and transplant surgeons. Over the past five to six decades advances in the field of transplant immunology have transformed solid organ transplantation into standard care, with excellent short term results in kidney, heart, lung, liver and pancreas transplantation.⁸ Most of these advancements have occurred through a better understanding of how the immune system works and as a result the development of more effective and less toxic drugs to suppress it. As with all multidisciplinary endeavours, each specialty brings with it its own language and terminology. In composite tissue allotransplantation (CTA) the immunologic principles of graft rejection and failure as well as the mechanism of action, routine regimens, dosages and toxicities of the drugs used to manipulate the immune system are far removed from the knowledge base of the general plastic surgeon.

Today, as the fields of reconstructive and transplant surgery again join forces to introduce and move hand and facial tissue allotransplantation into the clinical arena, it is important that surgeons in both disciplines have a working knowledge of the relevant scientific and technical principles in their respective fields. With this in mind, this manuscript provides plastic surgeons with a comprehensive and understandable review of some of the key immunological principles relevant in CTA. We accomplish this by providing the reader a brief history of CTA, current treatment approaches, risks associated with immunotherapy, and current avenues of research in CTA. A timeline with the history of CTA, illustrations of drug mechanisms and toxicity, a listing of hand and face transplants performed to date and a glossary of terminology (*italicised*

words throughout the text appear in the glossary) are also provided to make this review more comprehensible and useful to the reader.

The history of composite tissue allotransplantation (see timeline, Fig. 1)

*'The more sand that has escaped from the hourglass of our life, the clearer we should see through it.'*⁹

Jean Paul

A brief history of CTA

Pharmacological treatment to facilitate graft survival was described as early as the 5th Century BC.¹⁰ In 348 AD 'The legend of the black leg' (Leggenda Aurea) is the tale of twin brothers Cosmas and Damian who replaced the diseased leg of a sleeping man with that of a recently deceased Ethiopian Moor¹¹ and is credited with being the first known description of a CTA. During the Renaissance in Bologna, Italy, Gaspare Tagliacozzi, (1547–1599) described autotransplanting tissue from the arm to reconstruct a nose, and allotransplantation of the nose from a slave to his master. While the former procedure was reported to be successful, the latter one failed. Tagliacozzi described the problems he encountered with transplanting tissues from one individual to another in his 1596, 'De Curtorum Chirurgia per Insitionem', where he writes 'The singular character of the individual entirely dissuades us from attempting this work on another person. For such is the force and power of individuality, that if any one should believe that he could achieve even the least part of the operation, we consider him plainly superstitious and badly grounded in physical science'.

Over the next century, several reports of tissue transplants appeared periodically in the literature. However, the first substantiated short term successful allotransplant of note was that of sheep skin reported by Bunker in 1804.¹² From this time almost 100 years passed until Alexis Carrel described successful orthotopic hind limb transplants in dogs.¹³ As part of his work he developed a triangulation suturing method for anastomosing small blood vessels. For this and other research he was awarded the Nobel Prize in 1912.^{14,15} At the same time, Guthrie described heterotopic allotransplantation of dog heads, with documented good short term postoperative restoration of salivation and eyelid function.¹⁶ Inevitably this success was short-lived and the transplant was rejected. While these contributions laid the foundation for the development of the microsurgical techniques necessary for transplanting tissues, the immunological barriers were yet to be addressed.

The tragedies of war in the early 1940s provided the impetus for investigating immunological barriers associated

Table 1 Clinical hand and facial tissue transplants performed

Type of CTA	Date performed	Location	Institution	Recipient age & gender	Immunotherapy	Graft survival	Patient survival	Acute rejection	Chronic rejection
<i>Hand transplants</i>									
Single hand transplant	Feb-1963	Guayaquil, Ecuador	(*)	28 y/o male	Cortisone/ 6-mercaptopurine/ azathioprine (AZA) & hydrocortisone FK506/MMF/ prednisolone	(-) Rejection & removal 3 wks post transplant; due to insufficient immunosuppression (-) Rejection & removal of hand 2yrs 4mo post transplant; due to non-compliance (+)	(+)	(+)	(-)
Single hand transplant	Sep-1998	Lyon, France	Hopital Edouard Herriot	48 y/o male			(+)	(+)	(+)
Single hand transplant	Jan-1999	Louisville, USA	Jewish Hospital	37 y/o male	FK506/MMF/ prednisolone		(+)	(+)	(-)
Single hand transplant	Sep-1999	Guangzhou, China	Nanfeng Hospital	39 y/o male	FK506/MMF/ prednisolone	(-) Rejection & removal of hand 1 yr 8mo post transplant; unknown cause (+)	(+)	(+)	(-)
Single hand transplant	Jan-2000	Guangxi, China	1st Affiliated Hospital, Guangxi Univ.	27 y/o male	FK506/MMF/ prednisolone		(+)	(+)	(-)
Double hand transplant	Jan-2000	Lyon, France	Hopital Edouard Herriot	33 y/o male	FK506/MMF/ prednisolone		(+)	(+)	(-)
Digital transplant	Jan-2000	Yantai, China	Shandong Provincial Hospital	18 y/o male	(*)		(+)	(+)	(-)
Double hand transplant	Mar-2000	Innsbruck, Austria	Universitätsklinik für Chirurgie	45 y/o male	(*)		(+)	(+)	(-)
Single hand transplant	May-2000	Kuala-Lumpur, Malaysia	Selayang Hospital	1 mo/o female	None (Identical twin)		(+)	(-)	(-)
Double hand transplant	Sep-2000	Guangzhou, China	Nanfeng Hospital		(*)		(+)	(+)	(-)
Single hand transplant	Oct-2000	Milano, Italy	Milano-Bicocca University	35 y/o male	(*)		(+)	(+)	(-)
Double hand transplant	Jan-2001	Harbin, China	1st Affiliated Hospital, Harbin Medical Univ.	(*)	(*)		(+)	(+)	(-)
Single hand transplant	Feb-2001	Louisville, USA	Jewish Hospital	36 y/o male	FK506/MMF/ prednisolone		(+)	(+)	(-)
Single hand transplant	Oct-2001	Milano, Italy	Milano-Bicocca University	(*)	FK506/MMF/ prednisolone		(+)	(+)	(-)
Single hand transplant	Jun-2002	Brussels, Belgium	Erasme Univ. Hospital	(*)	(*)		(+)	(+)	(-)
Single hand transplant	Nov-2002	Milano, Italy	Milano-Bicocca University	(*)	FK506/MMF/ prednisolone		(+)	(+)	(-)
Double hand transplant	Feb-2003	Innsbruck, Austria	Universitätsklinik für Chirurgie	(*)	(*)		(+)	(+)	(-)

(continued on next page)

Table 1 (continued)

Type of CTA	Date performed	Location	Institution	Recipient age & gender	Immunotherapy	Graft survival	Patient survival	Acute rejection	Chronic rejection
Double hand transplant	May-2003	Lyon, France	Hopital Edouard Herriot	(*)	FK506/MMF/prednisolone	(+)	(+)	(*)	(-)
Single hand transplant	Nov-2006	Louisville, USA	Jewish Hospital	58 y/o male	FK506/MMF/prednisolone	(+)	(+)	(*)	(-)
Double hand transplant	Nov-2006	Valencia, Spain	Hospital La Fe	47 y/o female	FK506/MMF/prednisolone	(+)	(+)	(*)	(-)
<i>Facial tissue transplants</i>									
Cephalo-cervical skin flap & two ears	Sep-2003	Nanjing, China	Jinling Hospital	72 y/o female	FK506/MMF/prednisolone/Zenapax	(+)	(+)	(-)	(-)
Face transplant	Nov-2005	Amiens, France	Hopital Edouard Herriot	38 y/o female	FK506/MMF/prednisolone	(+)	(+)	(+)	(-)
Face transplant	Apr-2006	Xi'an, China	Xijing Hospital	30 y/o male	FK506/MMF/prednisolone	(+)	(+)	(*)	(-)
Face transplant	Jan-2007	Paris, France	Henri-Mondor Hospital	29 y/o male	FK506/MMF/prednisolone	(+)	(+)	(*)	(-)

*Data unavailable.

with tissue allotransplantation. A young plastic surgeon, Thomas Gibson, was hired by the British Medical Research Council to care for severely burned WWII pilots. While caring for these patients, Gibson noted accelerated rejection of skin grafts from the same donor that were transplanted on a second attempt at a later date.¹⁷ To make sense of these observations, he worked with zoologist and researcher Peter Medawar who, in animal experiments, demonstrated that specific characteristics of the rejection process, such as latency, memory, and specificity of graft destruction, were the consequence of an active immune response mounted by the recipient.¹⁷ These discoveries laid the groundwork for the development of the field of modern transplant immunology and consequently the development of the immunotherapy used today to prevent allograft rejection. For his contributions to the field Medawar received the Nobel Prize in medicine in 1960.

In the 1950s Joseph Murray, a plastic surgeon, studied skin and kidney transplants in dogs and later went on to perform the first successful human kidney transplant between identical twins.¹⁸ The late 1950s and early 1960s brought the discovery of agents such as azathioprine, 6-mercaptopurine and corticosteroids,¹⁹⁻²² which demonstrated prolonged graft survival in solid organ transplants in animal models. Unfortunately this same success could not be reproduced in CTAs containing skin tissue. In 1963, a team of surgeons in Ecuador performed the first human hand transplant (Table 1) but inadequate immunosuppression [azathioprine (AZA) and hydrocortisone] resulted in rejection and the hand had to be amputated 3 weeks post transplant.^{23,24} The introduction of cyclosporine A (CsA), in 1976 revolutionised the transplantation field by reducing acute rejection rates in kidney transplant recipients from 70 to 50% and increasing short term allograft survival rates from approximately 50 to 80% at 1 year.²⁵⁻²⁷ These positive results in heart, kidney, pancreas and liver transplantation^{28,29} led to renewed attempts to transplant hind limbs and mandible bone in small animal models and demonstrated reduced acute rejection and prolonged survival rates.³⁰ In the late 1970s and early 1980s three separate groups tested the efficacy of cyclosporine A in upper extremity transplants in primate models.³¹⁻³³ Although rejection was suppressed for periods of up to 300 days, in these experiments the highly immunogenic skin portions of transplanted extremities were rejected within the first few months after transplantation. These discouraging results together with the failed human hand transplant in Ecuador caused reconstructive surgeons to abandon further attempts to transplant hands for another decade. In the early 1990s cyclosporine-AZA steroid-based regimens were used in several clinical CTAs to reconstruct nerves,³⁴⁻³⁶ tendons,³⁷ muscle,³⁸ bone and joint,³⁹ and laryngeal defects.⁴⁰ More recently, additional clinical CTAs have been reported to reconstruct abdominal wall muscle,⁴¹ tongue and uterus.⁴² While the outcomes in these attempts have been reported to be generally positive, none of these CTAs contained skin and its associated appendages.

In the mid to late 1990s, with the goal of performing human hand transplants, researchers at the University of Louisville were evaluating a variety of approaches that maximised immunosuppression (to prevent 'skin' rejection) while minimising toxic side effects (due to the reluctance

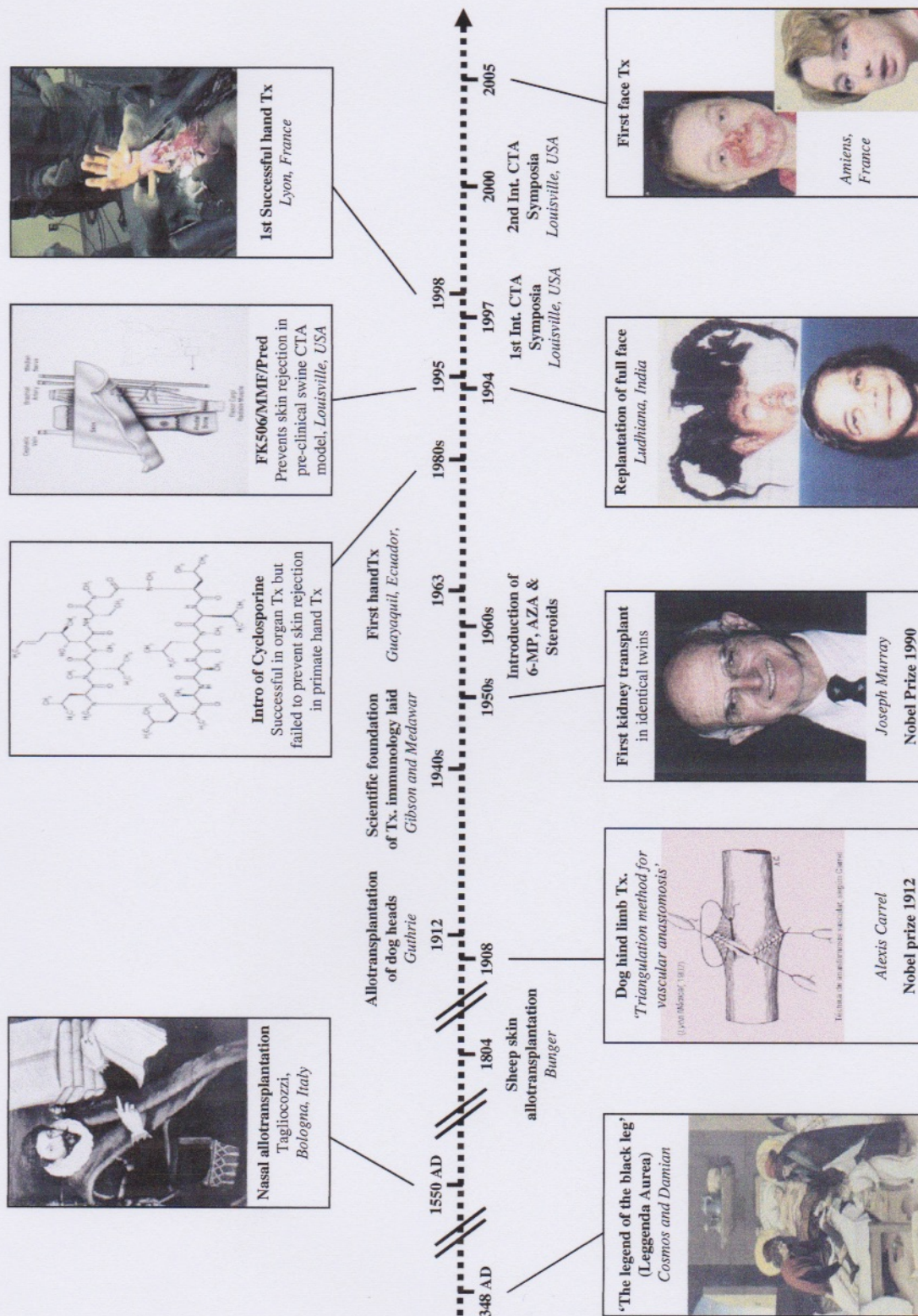


Figure 1 Composite tissue allotransplantation history timeline.

of hand surgeons to expose their amputee patients to the relatively high risks of immunosuppression). In keeping with these criteria several novel methods of local immunosuppression drug delivery were explored. These included topical drug applications, direct drug delivery using implanted pumps^{43–47} and magnetic drug targeting (attaching drugs to metal particles, infusing them systemically and then using a magnet placed over the transplanted allograft to localise the drug).^{48,49} Additional approaches that met the criteria of *maximal immunosuppression with minimal toxicity* were also studied: tolerance induction,^{50–53} low dose immunosuppression,⁵⁴ and lymph node removal.^{55,56} In one of these experiments investigating local drug delivery using implanted pumps in a pig forelimb CTA model,^{57,58} the control group consisted of animals receiving a drug regimen, considered at the time, and still today, to be the best treatment in clinical kidney transplantation (tacrolimus/*mycophenolate mofetil* (MMF)/corticosteroid). In this experiment the pumps (experimental group) malfunctioned, while the limbs of the controls animals, receiving the drug combination tacrolimus/MMF/corticosteroid orally, unexpectedly survived for the duration of the experiment with relatively low toxic side effects.^{59,60} Based on these findings the team in Louisville applied to their hospitals' institutional review board for approval to perform human hand transplants. These landmark experimental findings opened the door to performing human hand transplants, and between 1998 and 1999, teams in Lyon (France),⁶¹ Louisville (USA)⁶² and Guangzhou (China) performed the first four successful hand transplants using tacrolimus/MMF and corticosteroid combination therapy.⁶³ Today seven of 20 hand transplants performed worldwide are more than 8 years post transplant and only two graft failures have been reported, one due to noncompliance⁶⁴ and the other performed in China, due to unclear aetiology.² Overall the functional outcomes and patient satisfaction have been reported to be good.² The successful use of this tacrolimus/MMF/corticosteroid combination therapy in hand transplants has led other groups that had performed laryngeal, bone, nerve, and more recently facial tissue allotransplants,^{5,6,65} to use this same drug combination.

Immunotherapy approaches used in composite tissue allotransplantation

The ultimate goal and thus the focus of transplant immunology research is to effectively suppress rejection whilst minimising toxic side effects. In clinical practice this is achieved through a comprehensive balance of multiple drugs and methodologies that interfere with the immune response at various sites by blocking the formation, stimulation, proliferation, and differentiation of lymphocytes (Fig. 2). These drugs are administered immediately after transplanting the organ or tissues (*induction therapy*) and regularly thereafter 'for life' (*maintenance therapy*) and in response to rejection episodes (*treatment or rescue therapy*) (Table 2).

Induction therapy (Table 2)

The goal of *induction therapy* is to achieve immediate, profound immunosuppression for approximately 2 weeks post

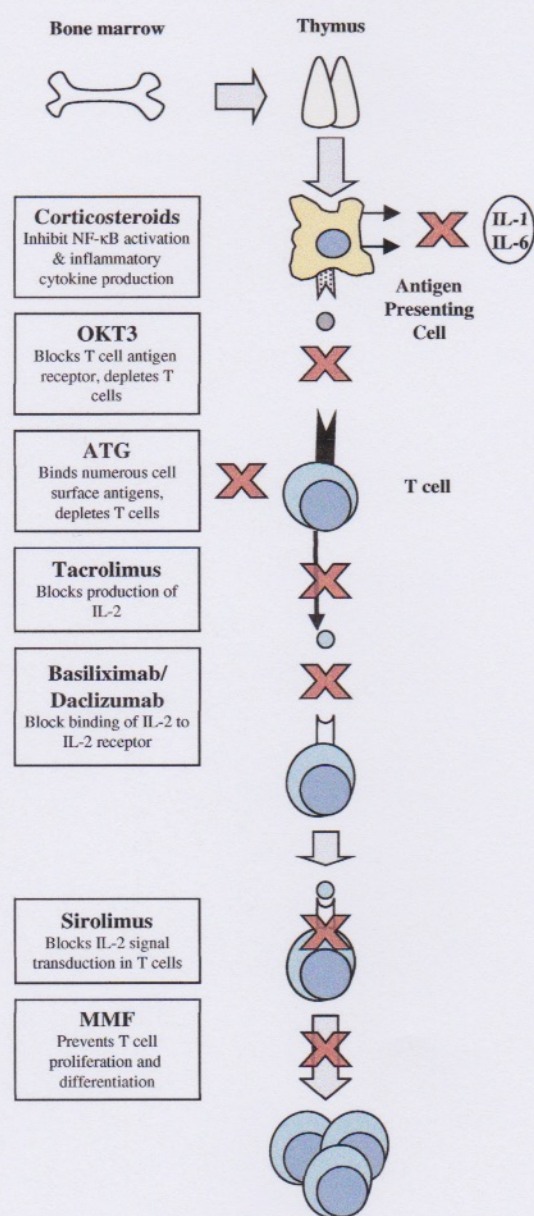


Figure 2 Mechanisms of actions of immunosuppressive drugs.

transplant to reduce the likelihood of *immediate rejection* (within 7–14 days post transplant) and early *acute rejection* (within 3–6 months after the transplant). Globally, induction therapy decreases the severity of the first rejection and delays the time to first rejection while allowing time immediately post transplant to achieve target immunosuppressive levels of the maintenance agents. The four primary drugs currently used clinically for induction therapy in solid organ transplants are: *polyclonal anti-thymocyte globulins* (ATG); *anti-interleukin-2 (IL-2) receptor monoclonal antibodies* (Daclizumab and Basiliximab); Campath-1H and *anti-CD3 monoclonal antibodies* (Table 2).⁶⁶ In addition to these drugs, donor bone marrow infusion has also been

Table 2 Immunosuppressive drugs and their associated toxicities

Therapy type	Drug	Class	Toxicities/adverse effects						
			Hyper-tension	Hyper-glycaemia	Nephro-toxicity	Hyper-lipidaemia	Malignancy	Infection	Other
Induction	Antithymocyte globulin (ATG)	Polyclonal antibody	Ø	Ø	Ø	Ø	++	+++	Anaphylactic reaction, serum sickness
	Anti-interleukin-2 receptor monoclonal antibodies (Daclizumab & Basiliximab)	Monoclonal antibody	Ø	Ø	Ø	Ø	Ø	+	Anaphylactic reaction (rare)
	Anti-CD3 monoclonal antibodies (OKT3)	Monoclonal antibody	Ø	Ø	Ø	Ø	++	+++	Anaphylactic reaction, pulmonary oedema
Maintenance	Tacrolimus (FK506)	Calcineurin inhibitor	+	++	++	+	+	++	Tremor, liver
	MMF (mycophenolate mofetil)	Anti-proliferative agent	Ø	Ø	Ø	Ø	+	++	Gastric, bone marrow
	Corticosteroids	Corticosteroid	++	+++	Ø	+++	Ø	+++	Osteoporosis
Treatment or rescue	Sirolimus (rapamycin)	TOR inhibitor	Ø	Ø	Ø	++	Ø/-	++	Proteinuria, bone marrow
	Corticosteroids (increased dosage)					See above			
	Tacrolimus (increased dosage)								
	Antibodies (increased dosage)								

KEY: + = mild, ++ = moderate, +++ = severe, Ø = none.

tried, on an experimental basis, for induction therapy. In an attempt to induce tolerance through *microchimerism*, the team in Amiens, France, transplanted donor derived bone marrow along with the facial tissues.⁴ While this approach has been reported to induce tolerance in an animal model^{67,68} its effectiveness in humans remains controversial. Post transplant assessments for the presence of tolerance in the facial tissue recipient in this case in France have been reported to be negative.⁶⁹

It is important to note that the use of induction agents has been stabilising primarily due to their efficacy in kidney transplantation with steroid minimisation regimens. T-cell depleting induction agents ATG and anti-CD3 monoclonal antibodies (OKT3) have been associated with increased infection and post transplant lymphoproliferative disorders (PTLD). In addition, induction agents have significant costs associated with their use.

Maintenance therapy (Table 2)

The goal of *maintenance therapy* is to reduce the immune system's ability to recognise and reject the foreign organ or tissue, while limiting toxicity. As the patient progresses further post transplant the risk of rejection is reduced

and the immunosuppressive regimen is tailored to the individual patient to provide lifelong suppression of the immune system with minimal toxicity. The primary drug combination used for *maintenance therapy* in hand and facial tissue allotransplantation is *tacrolimus (FK506)*, *mycophenolate mofetil (MMF)* and *corticosteroids* (see below).²

Treatment or rescue therapy (Table 2)

Corticosteroids are the first line of treatment in acute rejection episodes. However, when they are unsuccessful the same powerful antibody-based therapy used in induction is usually started. Rejection episodes have also been successfully treated with high-dose *tacrolimus* and *sirolimus (rapamycin)*. In hand and facial tissue allotransplantation *topical corticosteroids* and *topical tacrolimus* have also been used successfully.²

Combination therapy

In solid organ, hand and facial tissue allotransplantation, combinations of drugs are employed in dual, triple, or sequentially in countless variations. Contemporary protocols use a range of drugs, dosage schedules, administration methods, and monitoring guidelines.^{2,66,70} In most cases

each of the drugs used inhibits the immune system at different site(s). The overall effect of combining different drugs that act by different mechanisms is that a very powerful immunosuppressive effect is achieved. This makes it possible to administer low doses of each individual drug and thus reduce the drug-related toxicity. Due to its effectiveness in suppressing skin rejection and relatively low toxic side effects, tacrolimus-based combination therapy has become the immunotherapy of choice for hand and facial tissue allotransplantation.

Tacrolimus (FK506) introduction in 1992 led to a decrease in 1-year acute rejection rates from the previous 50% with cyclosporine-based immunosuppression to approximately 30%.⁷¹ Tacrolimus is a macrolide antibiotic, derived from the soil fungus *Streptomyces tsukubaensis*⁷² that prevents T-cell activation and suppresses B-cell activation and like cyclosporine is a *calcineurin inhibitor*. In vitro tacrolimus has been shown to be 100 times more potent than cyclosporine (Table 2; Fig. 2).⁷³ It is of interest that tacrolimus has been shown to promote nerve regeneration in small animal models after nerve injury.^{74,75} These effects seem to be related to actions of multiple *neuroimmunophilin ligands*⁷⁶ and may be of particular use in instances such as hand and facial CTA where motor and sensory function is crucial for overall function. In fact this effect of promoting nerve regeneration is thought to be responsible for the 'better than expected' early functional outcomes reported in the clinical hand and facial tissue allotransplants performed.^{2,4} As mentioned above, tacrolimus has also been used clinically in the form of a topical immunosuppressant for maintenance therapy and to reverse acute rejection episodes in both hand and face transplantation.^{2,4} Topical tacrolimus ointment is also used in the clinical setting to treat various skin conditions such as atopic dermatitis, psoriasis and pyoderma gangrenosum.⁷⁷⁻⁸⁰

Mycophenolate mofetil (MMF) introduction in 1995 resulted in the lowering of acute rejection rates.⁸¹ When combined with tacrolimus and corticosteroid, MMF provided 1-year acute rejection rates below 20%.⁸²⁻⁹² MMF is an antiproliferative immunosuppressive drug that selectively inhibits the rate-limiting enzyme inosine monophosphate dehydrogenase, required for de novo synthesis of guanosine nucleotide. This is essential for proliferation of T and B lymphocytes (Table 2; Fig. 2).

Corticosteroids are cytokine gene expression blockers and, along with adrenal glucocorticoids, are the most commonly used immunosuppression drugs. Prednisolone, the prototype in this class, is analogous to the major endogenous corticosteroid, cortisol (hydrocortisone), but four times more potent in its action. The actions are mediated by subcellular hormone receptors that form steroid receptor complexes, bind to DNA and affect the expression of genes driving protein synthesis and cellular processes (Table 2; Fig. 2).

Risks associated with immunotherapy

Immunosuppression-associated risks pose perhaps the greatest barrier to performing routine hand and facial tissue allotransplantation. The risks associated with the immunosuppressive drugs currently used in hand and facial tissue allotransplantation are well known, having been studied in

tens of thousands of organ transplant recipients over the past 15 years and more recently in hand (8 years) and facial tissue (1 year) transplant recipients. There are currently no objective means for evaluating the overall state of immunosuppression. As a result, clinical manifestations of under-immunosuppression (acute rejection) and over-immunosuppression (infection and malignancy) provide only general indicators of the degree to which the immune system is suppressed. In the following section we divide the discussion of immunosuppression-associated risks into three parts; risks of rejection, risks associated with immunosuppression and finally the perception of risk by affected populations.

Risks of rejection

Under-immunosuppression can lead to acute rejection. In human hand transplant recipients *acute rejection* rates were recently reported to be 67% at 1 year. In these cases all acute rejection episodes were successfully reversed regardless of the anti-rejection therapy used.² These high acute rejection rates observed in hand transplants (compared to kidney transplants) may be explained, in part, by the greater immunogenicity of skin tissue.^{1,64,93,94} In solid organ transplantation high acute rejection rates are often associated with high incidence of chronic rejection (see below) and low organ survival rates. However, this has not been the experience in hand transplantation. Despite the relatively high acute rejection rates observed in hand transplant recipients, survival rates have been high. This may be due to early detection (made possible by direct visual inspection of the skin) allowing immediate treatment and reversal of acute rejection episodes.

Chronic rejection is the most important cause of late graft loss in solid organ transplantation. While the mechanisms of chronic rejection have not been well defined, experience in solid organ transplantation indicates that high occurrence of acute rejection episodes coincides with higher incidence of chronic rejection.^{95,96} This has not been observed in human hand transplants. In one out of 20 hand transplants performed, clinical and histological characterisation of what was believed to be chronic (cutaneous) rejection was reported. In this single case, more than 2 years post transplant, the patient stopped taking his immunosuppression medication which led to graft failure and the hand had to be surgically removed.^{1,64} This relatively low occurrence of chronic rejection may be attributable to three main factors: (1) follow up is relatively short; (2) CTAs do not appear to be subject to vascular and parenchymal toxicity of immunosuppressive medication, as are kidney allografts; and (3) early recognition enabling early treatment and reversal of acute rejection. Additional evaluations of chronic rejection in human hand and facial tissue allotransplantation are needed to better define its risk and influence on long-term allograft survival.

Graft loss occurs when all attempts to reverse rejection fail and the decision is made to discontinue the immunosuppression medications. Graft loss has been reported in two out of 20 human hand transplants, one mentioned above, due to medication noncompliance at 2 years and 4 months post transplant⁶⁴ and the other due to uncertain aetiology (Table 1). The graft may also be 'lost' if a decision is made to surgically remove a viable graft in the presence

of drug toxicity, infection or malignancy, when saving the patient's life is clearly more important than saving the allotransplant. This situation has not been reported in any of the hand or face transplants performed to date.

Risks associated with immunosuppression in CTA

The primary complications associated with immunosuppressive therapy in solid organ transplantation are due to over-immunosuppression. These risks can be categorised into immunologic and nonimmunologic. The immunologic complications include malignancies, cardiovascular-related disease, nephrotoxicity, gastrointestinal adverse effects, diabetes and infection.

In the hand and face transplants performed to date, infection has been the main complication reported.² Of these, bacterial infections occurred at a rate of 12% (two infections: *Clostridium difficile* enteritis and *Staphylococcus aureus* osteitis), fungal infections occurred in 28% (all cutaneous mycoses without invasive disease) and viral infection in 34% of cases. Only 6% of patients experienced cutaneous herpes simplex infections. None of these infections resulted in graft or patient loss.² Post transplantation bone disease was reported in a single case of avascular necrosis of the hip.²

Nonimmunologic risks

Nonimmunologic risks are primarily due to adverse effects of immunosuppressive and prophylactic agents used in transplant recipients. Immunosuppressive agents may increase cardiovascular risk⁹⁷ by affecting cholesterol levels, triglycerides,⁹⁸ blood pressure,⁹⁹ renal dysfunction and post transplant diabetes mellitus.^{98,100} While post transplant diabetes mellitus has not been reported, transient hyperglycaemia occurred in 50% of the hand transplant recipients, primarily while receiving high corticosteroid doses early after transplantation.²

Noncompliance was a problem in one of 20 patients and this could possibly have been avoided had a more careful pre-transplant psychosocial screening assessment been performed. Overall, with a post transplant follow up of 8 years in human hand transplantation, the incidence of graft failure and complications has been low while functional and aesthetic recovery has been described as good (Table 1).

Immunosuppressive risk acceptance in CTA

Ultimately patients will decide whether the risks of immunosuppression justify the benefits of hand and face allotransplantation. In a study that questioned facially disfigured individuals (who could benefit from a face transplant), kidney transplant recipients (who live with the risks of immunosuppression), and healthy controls on the amount of risk they would accept to receive several types of non-life-saving transplant procedures, all respondents would accept the most risk to receive a face transplant. When provided a list of 20 potential immunosuppressive side effects, 77% of facially disfigured respondents, 93% of kidney transplant recipients, and 86% of the controls would be willing to undergo face transplantation.¹⁰¹ When asked if they would opt for face transplantation if the possibility of

rejection within 1 year was 50%, 71% of facially disfigured persons, 88% of organ transplant recipients, and 87% of non-affected individuals said 'yes'.¹⁰¹ These findings indicate that both affected and non-affected individuals view the risks of a face transplant as more acceptable than other non-life-saving treatments including kidney transplantation, a standard treatment for which there is no comparable debate.

Current and future avenues of research in CTA

The ideal immunosuppressive strategy would be a combination of agents that are selective and specific in function, synergistically active for maximal effectiveness, free of toxic reactions, easy to administer, and inexpensive. To date, no ideal immunosuppressive drug has been developed. Continued research has ensured the introduction of more effective and less toxic immunosuppressant options. Despite this effort, currently available agents still fall short of being ideal. Several promising drugs in development include a once daily formulation of tacrolimus (Prograf®); LEA, a co-stimulatory blocking agent; and ISATX247, a small molecule calcineurin inhibitor with a potentially improved toxicity profile.

Immunologic *tolerance*, introduced by Medawar as 'actively acquired tolerance' in the early 1950s, could potentially eliminate the need for immunosuppressant drugs. This approach would minimise or potentially even eliminate the need for long-term immunosuppression and the risks associated with it.

While tolerance has been demonstrated using a variety of different protocols in animal models,^{102,103} to date, widespread clinical applicability of these protocols has been impeded due to the toxicity of the methods required to induce tolerance and the lack of successful studies in large animals.^{104,105}

Hand and facial tissue composite tissue allotransplantation is now a clinical reality with encouraging early results.²⁻⁷ As in the past, this advancement has been achieved through close collaboration with transplant immunologists. The development of new drugs designed to maximally and selectively suppress the immune system, while at the same time causing minimal toxic side effects, has made CTA a viable reconstructive treatment option. In this paper we have reviewed key terminology, drug combinations, mechanisms of immunosuppression and the risks associated with CTA. Plastic surgeons play a central role in treating facially disfigured individuals and will thus lead the development of these new reconstructive treatments. Accordingly, it is important that they be informed of the issues discussed in this manuscript. Informed consent, taking into account both individual and process factors, is critical when one discusses radical new procedures with patients.¹⁰⁶ We hope this paper will serve as a reference for the readership to consider and discuss CTA with their colleagues and patients.

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- resulting in platelet aggregation, fibrinoid necrosis of media arteries, and vascular obstruction.
- Azathioprine (AZA):** The imidazole derivative of 6-MP which is cytotoxic. AZA is converted in the liver to 6-MP which in turn resembles inosine monophosphate and causes fraudulent feedback inhibition of the early enzymes catalysing the cellular synthesis of DNA.
- Calcineurin inhibitor:** These drugs exert their effects through regulation of cytokine production. Cyclosporin A was the prototype in this class, used since the 1950s, and in the mid- to late-1980s tacrolimus (FK506) was introduced into clinical practice.
- Chronic rejection:** Rejection occurring months to years post transplant. Graft injury by immunological and non immunological factors.
- Combination therapy:** Combinations of drugs are used, with the goal of inhibiting different aspects of the immune response. The overall effect of this approach is a very powerful anti-rejection effect thus making it possible to administer low doses of each individual drug.
- Cyclosporin:** Cyclosporin A is a fungal metabolite from *Tolypocladium inflatum* gams. Its immunosuppressive action is due to the suppression of IL-2 production by T-cells.
- Hyperacute rejection:** Rejection occurring in the first few minutes post transplant. It is an antibody-mediated process via MHC. Damage to endothelial cells and small arterioles leads to microvascular blockage and graft failure.
- Induction therapy:** Silencing of the immune system for approximately 2 weeks post transplant to reduce the likelihood of acute rejection.
- Maintenance therapy:** Intermediate term (>2 weeks post induction) reduction of the immune system's ability to recognise and reject foreign tissue, reducing the risk of chronic rejection, whilst allowing sufficient remaining host defences to defend against infections and reduce the likelihood of malignant transformation.
- Mixed chimerism:** Refers to the coexistence of donor and recipient haematopoietic cells, with donor representation that can be detected by non-PCR-based techniques. The state of mixed chimerism can also be referred to as macrochimerism.
- Microchimerism:** The presence of two genetically distinct and separately derived populations of cells, one population being at a low concentration, in the same individual or an organ such as the bone marrow.
- Neuroimmunophilin ligands:** Neuroimmunophilin ligands are a class of compounds that hold great promise for the treatment of nerve injuries and neurological disease which act via unique receptors to afford neuroprotective and neuroregenerative properties via different mechanisms.
- Tolerance:** Donor-specific unresponsiveness without the need for combined immunosuppression - A situation where the recipient does not mount an immune response against the allograft but remains fully immunocompetent.
- Treatment:** Specific agents used to treat or suppress episodes of acute rejection.

Glossary of terminology

Acute rejection: Rejection occurring within the first three months post transplant. Mediated by the primary activation of T-cells